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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,492	06/23/2003	Robert John Mark	AM100012-P2	4877

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WYETH
PATENT LAW GROUP
5 GIRALDA FARMS
MADISON, NJ 07940

EXAMINER	
SHIN, DANA H	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,492	MARK ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7 and 8* is/are pending in the application.

4a) Of the above claim(s) *8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-23-2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Applicant's Election/Remarks

Applicant's election with traverse of Group I, consisting of claims 1-3 and 7, in the reply filed on February 28, 2006 is acknowledged. Applicant's arguments, see page 4, filed on February 28, 2006, with respect to withdrawing restriction between SEQ ID NO: 3 and SEQ ID NO:4 have been fully considered and are persuasive. The restriction between SEQ ID NO: 3 and SEQ ID NO:4 has been withdrawn. Claim 8 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 28, 2006, and cancelled claims 4-6. Accordingly, claims 1-3 and 7 are under examination.

Specification

The disclosure is objected to because of the following informalities: The instant specification discloses brief description of the drawings (pages 6-7) for Figures 1-13. However, the instant drawings include Figures 1-17. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ

761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2 and 7 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 7 of U.S. Patent No. 6,664,068 B2 in view of teachings of US 2002/0132788 A1.

Claims 1-2 and 7 of instant application are drawn to an siRNA molecule which inhibits the expression of a Pablo polypeptide of SEQ ID NO:2, wherein the molecule inhibits apoptosis in a eukaryotic cell.

Claims 1 and 7 of U.S. Patent No. 6,664,068 B2 are stated below:

> 1. An antibody which binds a Pablo polypeptide comprising an amino acid sequence of SEQ ID NO:2, wherein the antibody inhibits a Pablo/Bcl-xL binding interaction.
>
> 7. An antibody as in one of claims 1-6, wherein the antibody inhibits apoptosis.

US 2002/0132788 A1 teaches the following (column 3, paragraph 0036):

[0036] In a preferred embodiment, we provide a process for inhibiting gene expression in post-embryonic mammalian cells in vivo by delivering to a mammalian cell a siRNA comprising a double-stranded structure having a nucleotide sequence substantially identical to a sequence contained within the target gene and verifying the inhibition of expression of the target gene.

It would have been obvious to one of ordinary skill in the art to substitute the antibody of claims 1 and 7 of U.S. Patent No. 6,664,068 B2 for the siRNA of US 2002/0132788 A1, in order to inhibit the expression of already disclosed sequence of the Pablo SEQ ID NO:2 of U.S. Patent No.

6,664,068 B2, thereby inhibiting apoptosis. Since an siRNA inhibits gene expression at the post-transcriptional level in a nucleotide sequence specific manner and thus can be used as a gene therapy tool unlike an immunogenic antibody that binds an antigenic epitope, an siRNA is generally viewed as a more effective tool for suppression of a target gene. Furthermore, one of ordinary skill in the art would have known at the time of instant inventions were made that inhibition of the Pablo peptide expression can be achieved by means of either antibody or siRNA. Accordingly, one of ordinary skill in the art would have been motivated to utilize the siRNA technology in place of the antibody to inhibit Pablo expression. In light of this, it is concluded that instant claims 1-2 and 7 are not patentably distinct from claims 1 and 7 of U.S. Patent No. 6,664,068 B2.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional

application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos. 09/858,155 and 09/425,501, fail to provide adequate support in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Neither of the prior-filed applications stated above discloses use of small interfering RNA molecules targeted to Pablo, which inhibits Pablo expression via RNAi mechanism resulting in apoptosis in a cell. Furthermore, claimed inventions of instant claims 3 and 7, which set forth using SEQ ID NOs:3 and 4 that comprise 21 nucleotide-long double-stranded siRNA sequence, are not disclosed in the prior-filed applications.

For the reasons stated above, the priority of the prior filed applications is thus denied, and the filing date of instant application, June 23, 2003, will be the effective filing date for instant claims 1-3 and 7.

If applicant believes that the claimed subject matter in claims 1-3 and 7 of the instant application is disclosed in the prior-filed applications to which applicant claims the benefit under 35 U. S. C. 120, applicant is advised to point out the particulars in response to this Office Action.

Claims 1-3, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhou et al. (Nucleic Acids Research, April 1, 2002).

Claims 1-3 and 7 are directed to an RNA molecule having a sense strand nucleotide sequence of SEQ ID NO:3 and an antisense strand nucleotide sequence of SEQ ID NO:4, wherein the sequences are as follows:

RNA Artificial siRNA SEQ ID NO:3 **cgu**guggac**c gu**uuuaucugu u

RNA Artificial siRNA SEQ ID NO:4 cagauaa**acg** guccac**acgu** u

In particular, claim 3 is directed to any number of nucleic acids of each strand comprising SEQ ID NOs:3 and 4, because the instant claim recites "**a** sense strand nucleotide sequence of SEQ ID NO:3" and "**an** antisense strand nucleotide sequence of SEQ ID NO:4", in which both sequences embrace any fragment thereof comprising any portion of SEQ ID NOs:3 and 4.

Zhou et al., teach use of siRNAs in mediating post-transcriptional suppression of cyclins B1 and B2 in Xenopus embryos. They disclose siRNA sequences, wherein B1A5 comprises nucleotides "CGU" (page 1665, Materials and Methods: RNAs) which also comprise fragments of SEQ ID NO:3, and similarly, a complementary sequence B1A3 comprises nucleotides "ACG" which also comprise fragments of SEQ ID NO: 4, as indicated by bold-faced type above.

Claims 1-3 and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Brown et al. (US 2003/0166282 A1, effective filing date: Feb. 1, 2002).

Brown et al., teach the sense strand and the antisense strand of an siRNA molecule targeting the c-myc mRNA known as SEQ ID NOs:3 and 4, respectively (Column 14, Table 1), and are shown below:

5' UTR sense SEQ ID NO:3 GGGAGAUCCGGAGCGAAUAdTdT
5' UTR anti-sense SEQ ID NO:4 UAUUCGCUCCGGAUCUCCCdTdT

As shown above, "GGA" of the sense strand of SEQ ID NO:3 of Brown et al., comprise a portion of SEQ ID NO:3 of instant claim 3. Similarly, "UCC" of the antisense strand of SEQ ID NO:4 of Brown et al., comprises a portion of SEQ ID NO:4 of instant claim 4.

Claims 1-3 and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Khvorova et al. (US 2005/0246794 A1).

Khvorova et al., teach siRNA sequences that targets luciferase (Column 23, Table 3), wherein all siRNA duplexes are referred to by sense strand, and are shown below:

Luc 31 SEQ. ID 0241 U*GUGGAC*GAAGUACCGAAA

Luc 32 SEQ. ID 0242 UUU*GUGGAC*GAAGUACCGA

Luc 33 SEQ. ID 0243 UGUUU*GUGGAC*GAAGUACC

Luc 34 SEQ. ID 0244 UGUGUUU*GUGGAC*GAAGUA

Luc 35 SEQ. ID 0245 GUUGUGUUU*GUGGAC*GAAG

Luc 36 SEQ. ID 0246 GAGUUGUGUUU*GUGGAC*GA

Luc 37 SEQ. ID 0247 AGGAGUUGUGUUU*GUGGAC*

The nucleotide sequences italicized above correspond to the portion comprising "GUGGAC" of the SEQ ID NO:3 of instant application.

Claims 1-2 and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Mark et al. (US 2003/0215852 A1, effective filing date: April 1, 2002).

Claims 1-2 and 7 are drawn to an siRNA molecule, wherein the siRNA molecule inhibits the expression of a Pablo polypeptide of SEQ ID NO:2 in a eukaryotic cell, wherein the molecule inhibits apoptosis in the cell.

Mark et al., teach use of a Pablo siRNA molecule in S2 cells, CHO-K1 cells and in mice to inhibit Pablo production and expression (Columns 34- 36). They disclose the Pablo polypeptide SEQ ID NO:10 (Columns 47-48), which is identical to SEQ ID NO:2 of instant application. They further

disclose a nucleic acid sequence SEQ ID NO:9 (Column 46). Mark et al., also teach that Pablo is implicated in apoptosis (Column 5).

Teachings of Mark et al., therefore, read on and anticipate every element of the instant claims 1-2 and 7.

The applied reference, Mark et al. (US 2003/0215852 A1), has common inventors and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagase et al. (Applicant's citation number 15, submitted form 1449/PTO), in view of Zamore et al. (Cell, 2000), and Miki et al. (Applicant's citation number 13, submitted form 1449/PTO).

Claims 1-2 and 7 are drawn to an siRNA molecule, wherein the siRNA molecule inhibits the expression of a Pablo polypeptide of SEQ ID NO:2 in a eukaryotic cell, wherein the siRNA inhibits apoptosis in the cell.

Nagase et al., teach cloning of a gene called KIAA0269, which comprises 559 amino acids. The amino acid sequence of KIAA0269 of Nagase et al., is identical to entire SEQ ID NO:2 of the Pablo amino acid sequence (1-559) of the instant application. Nagase et al., also disclose highly enriched expression of KIAA0269 in human brain tissue (Table 3), which is the expression profile of Pablo. Nagase et al., do not teach use of KIAA0269 (or applicant's instant Pablo) sequence for designing an siRNA molecule to inhibit its expression in a eukaryotic cell.

Zamore et al., teach use of double stranded RNAs comprising 21-23 nucleotides of the target sequence in Drosophila lysates, which result in sequence-specific interference of Rr-Luc mRNA *in vitro*.

Miki et al., teach identification of WAVE (Wiscott-Aldrich syndrome protein) which has the identical amino acid sequence of KIAA0269 of Nagase et al. (page 6933, Figure B and Results). They teach that WAVE (or KIAA0269 or applicant's instant Pablo) is implicated in actin reorganization via WAVE over-expression studies. They demonstrate that WAVE functions downstream of Rac via dominant-negative mutant construct studies. They also confirm Nagase et al's teachings with respect to highly enriched expression of WAVE (or KIAA0269 or applicant's instant Pablo) in brain.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the 21-23 double-stranded target-specific RNA molecule in a eukaryotic cell as taught

by Zamore et al., in order to inhibit expression of Pablo in a eukaryotic cell comprising the Pablo cDNA sequence as taught by Nagase et al. and Miki et al.

One of ordinary skill in the art would have been motivated to study Pablo by inhibiting its expression via siRNA because defective actin reorganization has been implicated in a number of diseases such as Wiskott-Aldrich syndrome as taught by Miki et al. Because Miki et al., expressly teach that WAVE expression/function is inhibited by dominant-negative mutant WAVE, and Zamore et al., teach that an siRNA molecule suppresses gene expression/function in a sequence-specific manner, one of skill in the art would have been motivated to suppress Pablo expression/function in cells via siRNA molecule in lieu of dominant-negative mutant construct of Miki et al., in order to investigate biological roles of Pablo in actin reorganization-related cellular events and to elucidate Pablo signaling pathways as taught by Miki et al.

Since the methods of making and using the siRNA molecule of Zamore et al., the sequence encoding Pablo mRNA/protein of Nagase et al. as well as Miki et al., and the benefit of employing gene knock-down experiments in elucidating Pablo's cellular roles/signaling pathways using inhibitors such as dominant-negative constructs of Miki et al., were known at the time of inventions of claims 1-2 and 7 were made, one of ordinary skill in the art would have been motivated to practice the siRNA-mediated knock down of Pablo gene expression/function with reasonable expectation of success.

Therefore, the invention of claims 1-2 and 7, taken as a whole, is *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Dana Shin
Examiner
Art Unit 1635

dhs
March 30, 2006

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER